REMARKS

Claims 9 and 11-25 are pending in the case. Claims 23 and 24 have been amended to correct errors in dependency. Claims 9, 11-22 and 25 remain unchanged. No new matter has been introduced.

Claims 9 and 11-25 are rejected under 35 U.S.C. §103(a) as being unpatentable over WO 93/11733 (Carling) in view of Cazzola et al. (Reference U), Nederlands Tijdschrift voor Geneeskunde (Reference V) and Saunders Manual of Medical Practice (Reference W).

Claim 9 recites a method of treating chronic obstructive pulmonary disease (COPD) by administering to a patient formoterol (or a salt, a solvate of such a salt, or a solvate of formoterol) and budesonide.

As discussed in Applicants' previous response, Carling does not teach or suggest that his combination of formoterol and budesonide is suitable for treating COPD. Carling mentions that the combination is suitable for use in treating "respiratory diseases." The only specific respiratory disease that is mentioned in the Carling specification is asthma.

As also discussed previously, the suitability of the formoterol/budesonide combination for treating COPD would not have been obvious in view of Carling's general teaching of its use in treating respiratory diseases, even if this teaching could have been properly combined with the teachings, in References (U) and (V), respectively, that formoterol and budesonide alone would be useful in the treatment of COPD, and the mention in Reference (W) that COPD is a respiratory disease.

In response to these arguments, and the data submitted by Applicants' with their previous response, the Examiner has maintained the rejection made in the previous office action, on the grounds that "there is no independent data by which the Examiner can make a reasonable determination of [whether a] synergistic effect is present [or] the combination of budesonide/formoterol gives greater than additive effect in treatment of COPD."

Applicants submit herewith data that provide evidence of a strong synergistic effect for the budesonide/formoterol combination.

A placebo-controlled 12 month clinical trial was performed using the claimed combination of budesonide/formoterol (under the product name Symbicort®) in the treatment of moderate to severe COPD. 1022 patients were treated in a 2 week initial period with oral prednisolone (30 mg once daily) and formoterol (2 x 4.5 μg twice daily). The patients had the following profile:

Age $\geq$ 40 years

COPD patient for at least 2 years

At least 10 pack years smoking history[1]

Documented use of inhaled bronchodilators as a quick relief medicine

At least one severe COPD exacerbation within 2-12 months of entry

$FEV_1 \leq 50\%$ predicted normal, pre-bronchodilator

$FEV_1/VC \leq 70\%$ pre-bronchodilator

(FEV_1 = Forced Expiratory Volume within 1 second, VC = vital capacity)

The patients were randomized into four groups and treated as follows:

Group 1: Budesonide/formoterol combination (Symbicort® inhaler) at a dosage of 2 puffs, each puff containing 160 μg budesonide/4.5 μg formoterol, twice per day

Group 2: Budesonide alone (2 puffs, each containing 200 μg budesonide (metered dose, equivalent to the 160 μg dose in the Symbicort® inhaler), twice daily)

Group 3: Formoterol alone (2 puffs, each containing 4.5 μg formoterol, twice daily)

Group 4: Inhaled a placebo composition (2 puffs, twice daily, no active ingredients)

The patients were studied for 12 months, with various measures of COPD symptoms being regularly recorded. The results of this study showed a synergistic effect from the combination of budesonide and formoterol.

For example, as shown in the graph titled "Symbicort Reduces No. of Severe Exacerbations/Patient/Year"[2] (Appendix 1, submitted herewith), as compared to the placebo

[1] As understood in the art, "10 pack years" indicates that the individual smoked a pack a day for 10 years, or 2 packs a day for 5 years, etc.

(Group 4), treatment with formoterol alone (Group 3) increased the number of exacerbations slightly (+3%), and treatment with budesonide alone (Group 2) decreased the number of exacerbations by 12%. Thus, it would be expected that the additive effect of the budesonide/formoterol combination would be a 9% reduction in exacerbations. Instead, Group 1, treated with the budesonide/formoterol combination, exhibited a 24% reduction in exacerbations.

A synergistic effect was also observed in the morning peak expiratory volume (PEF) of the patients, as shown in the graph titled "Symbicort Improves Morning PEF" (Appendix 2, submitted herewith). The difference in adjusted mean change of morning PEF, as compared to the placebo, was 3.5 L/min for the patients treated with budesonide alone, 11.1 L/min for those treated with formoterol alone ($p<0.001$), and 18.3 L/min for the patients treated with the budesonide/formoterol combination, i.e., 3.7 L/min higher than the additive result that would have been expected.

In view of the above, Applicants respectfully request that the rejection under 35 U.S.C. §103 be withdrawn.

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[2] Severe exacerbations were considered to be exacerbations requiring medical intervention, i.e., administration of antibiotics and/or oral steroids, and/or hospitalization due to respiratory symptoms.

Applicants ask that all claims be allowed. Attached is a marked-up version of the changes being made by the current amendment. Enclosed is a $110.00 check for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 06275-150003.

Respectfully submitted,

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Version with markings to show changes made

In the claims:

Claims 23 and 24 have been amended as follows:

23. (Amended) A method according to claim [1] 9 wherein the amount of the dose of the second active ingredient is from about 0.1 to 5 μmol.

24. (Amended) A method according to claim [1] 23 wherein the amount of the dose of the second active ingredient is from about 0.15 to 4 μmol.